Cannabis & Cannabinoids

- 400+ compounds [60 active cannabinoids] in marijuana plant (*cannabis sativa)*
- Cannabinoids most concentrated in stalks, leaves, seeds of plant, & in oily resin of F plant
- Delta (9)-tetrahydrocannabinol (THC) is most potent cannabinoid
- Others: delta (8)-THC, cannabinol & cannabidiol
- THC content in MJ has risen 7- to 15- fold since 70s: 150+ mg/joint in 2000
- Most studies of THC involve 10-25 mg doses common in 1970s
- Smoked MJ also has tars & aryl hydrocarbons (carcinogens)

THC Pharmacokinetics

- 50% of dose absorbed in lung; less in GI tract
- 1st pass effect w/GI absorption→lower THC levels
- Tissue distribution rapid: fat soluble so [fat] influences
- Entry into lipid [fat]-rich brain areas [cortex, amygdala/hippocampus, sensory, & motor] rapid
- Fatty tissue/brain levels peak 4-5 days post dose
- Half life of single dose of THC in blood is 4-6 hr
- BUT: Slow fat release & redistribution to tissue [brain etc], so elimination half life is much slower
- Liver metabolism [11-OH-THC major metabolite]
- Renal and gut excretion
- Poor correl'n of intox. & plasma/urine THC levels
- Urine levels + 1-2 d after 1 joint; 30-42 d if chronic

Cannabinoid Receptors: Discovery and Subtypes

- Present in brain cell membranes, as discovered in binding assays in 1988 by Devane et al.
- Two membrane-linked cannabinoid receptors now identified:
  - CB1 [in brain & peripheral nerves]
  - CB2 [in spleen & immune/inflammatory cells]
- Binding to CB1 and CB2 receptors activates intracellular G proteins & protein kinases, and inhibits adenyl cyclase, and then alters gene expression in the cells

Cannabinoid Receptor Binding Compounds In Brain Tissue

- Normal brain found to make its own receptor binding compound, arachidonylethanolamide, named anandamide [Sanskrit, “internal bliss”] in 1992
- Normal brain makes several other such endogenous ligands that bind to CB1 and CB2 receptors, acting just like THC
- They are chemically related to prostaglandins, i.e. fatty molecules involved in inflammatory responses

CB1 & CB2 Receptors: Locations & Effects

Region	THC and anandamide effect
spinal cord	analgesia [dynorphin and leu-enk released]
medulla	anti-emesis
VTA	reinforcement, DA release
cerebellum	incoordination
basal ganglia	slowed movement @ low [THC]
	increased movem't /catalepsy- hi [THC] NO?
thalamus	altered movement perception
hypothalamus	increased appetite, hypothermia NO?
hippocampus	impaired declarative memory
amygdala, PFC	reduced anxiety [low dose]
	increased anxiety [hi dose]
gut	reduced acid secretion, slow motility
spleen/immune	alters cytokines, inhibits T cell activation

NO? = nitric oxide perhaps involved

Cannabinoids: Effects on other transmitters

- Anandamide enhances DA release in PFC and VTA in naloxone-inhibitable fashion: reinforcing
- Possible role of endogenous cannabinoid and opiate systems in motivation & reinforcement; potential for therapeutic effect in schizophrenia, depression, etc?
- Interaction with Acetyl choline & GABA systems
- CB1 activation may play a role in alcohol tolerance

Cannabis & Cannabinoids: Intoxication

Vasodilation [low BP, red eyes] & tachycardia

Low dose [2.5-300 mg] -> decreased anxiety, alertness, depressio and tension, and increased sociability (if taken in friendly surroundings) starting in minutes and lasting 2-4 hr.

Cannabis can produce

- dysphoria [panic, paranoia, psychosis]; risks: high dose, naïve user, anxiet schizophrenia,
- altered perceptions [enhanced emotional effects] ,
- rapid time perception, and occasionally
- hallucinations

Impaired recall [7+d] & motor performance at low [5-10 mg] doses

Increased MVAs, MVA deaths, traumatic deaths, & pilot errors for 24+ hr after dose

Cannabis & Cannabinoids: Chronic Toxicity & Dependence

- No reported deaths
- Euphoric tolerance [d/t receptor down-regulation?]
- Withdrawal [craving for marijuana, decreased appetite, sleep difficulty, aggression, anger, irritability, restlessness, and strange dreams] occurs after 1 joint/d for > 10 days [involves opiate system/preproenk.]
- Increased rates of bronchitis, COHgb, lung CA?
- Memory and other cognitive problems resolve within 6-12 weeks after cessation of chronic, very heavy use (5,000+doses)

Medical uses of cannabinoids

Marinol: FDA approved for treatment of appetite loss and fatigue in cancer and AIDS patients

Requirements for cannabis or CB1 receptor agonists to have therapeutic potential:

- **Efficacy of clinical significance in selected patients & conditions; debate re: unique efficacy**
- **Freedom from addiction, psychomotor, and other significant risks**
- **Minimal drug interactions**

Stimulants: Cocaine and Amphetamines

Cocaine: forms & absorption

Many alkaloids in *coca*, chewed by Andeans for centuries

- **Absorption via buccal mucosa (oral tissue)**
- **Gastric acid inactivates cocaine, yielding low blood levels after swallowing**

Cocaine easily purified alkaloid, typically as white HCl salt

- **Nasal snorting: initial dose rapidly absorbed across venous plexus in nose**
- **Repeated doses less well absorbed due to cocaine-induced plexus vasoconstriction**
- **Intravenous dosing yields much higher blood levels**

After cocaine HCl extracted with water/ether or removed by boiling with $NaHCO_3$ [baking powder/sodium bicarbonate], get crystalline cocaine hydroxide, or "free base" cocaine. Cracks when heated

- **Cocaine HCl not volatile, but cocaine base is volatile on heating**
- **Volatility leads to high cocaine levels in heated vapor→ rapid absorption in lung after free base/crack smoking**

Amphetamines: forms & absorption

Most are oral pills (dexedrine, methamphetamine, methylphenidate)

- Low dose use appears to have little addictive potential (e.g., Ritalin)
- High dose use has moderate addictive potential

Methamphetamine (crystal meth, ice)

- Nasal snorting: initial dose rapidly absorbed across venous plexus in nose
- Little vasoconstriction, so repeated use yields good absorption
- Intravenous dosing yields much higher blood levels

Smoked

- Usually methamphetamine
- Volatility leads to high amphetamine levels in heated vapor→ rapid absorption in lung after smoking

Cocaine Pharmacokinetics

- **Tissue distribution rapid: blood flow & [fat] influence**
- **Rapid brain entry [cortex, amygdala] esp after IV and crack**
- **Enzymatic breakdown via hydrolysis by serum esterase**
- **Half life of cocaine in blood is 4-6 hr**
- **Liver metabolism [benzoylecognine (BE) major metabolite, half life 9 hrs]**
- **Renal excretion**
- **Urine levels of BE pos 1-2 d after single IV dose and 7-14 d post chronic high-level use**

Cocaine Receptor: Dopamine Transporter

- Cocaine receptor shown to be dopamine [DA] transporter [DAT], which mediates most of its behavioral effects
- DAT binding by cocaine thus results in dose-dependent increases in DA in synaptic cleft, enhancing DA effects
- DAT concentrations highest in motivational (VTA, Nucleus Accumbens) and motor control (caudate, putamen) areas of brain
- Mutations in DAT gene renders animals unresponsive to psychomotor stimulant properties of cocaine, but hyperactive at baseline: hyperactive behavior
- Cocaine also has high affinity for reuptake sites for serotonin and norepinephrine

Amphetamine: DA mechanisms of action

- Blocks DA reuptake at dopamine [DA] transporter [DAT
- Increases DA release from pre-synaptic sites

Cocaine: Pharmacodynamic Effects

- Local anesthesia [nasal, oral mucosa] and vasodilation
- Marked euphoria associated with rate of DAT blockade in N. Accumbens
- Reinforces self-administration behavior, leading to repeated use
- Sensitization: re-exposure enhances effect→can lead to behavioral pathology e.g., paranoia, hallucinosis
- Unclear if tolerance to reward effects develops in humans
- Increased physical activity and parkinsonian tremor (lasts 3+ months)
- Mild tachycardia (10/min) and hypertension (20/10)
- Coronary vasodilation, then vasoconstriction; also platelet activation and coronary thrombosis, increasing risk of stroke and MI
- Kindling and seizure induction
- Sleep disturbance

From Bozarth and Wise (1985) "Toxicity associated with long-term intravenous heroin and cocaine self-administration in the rat"

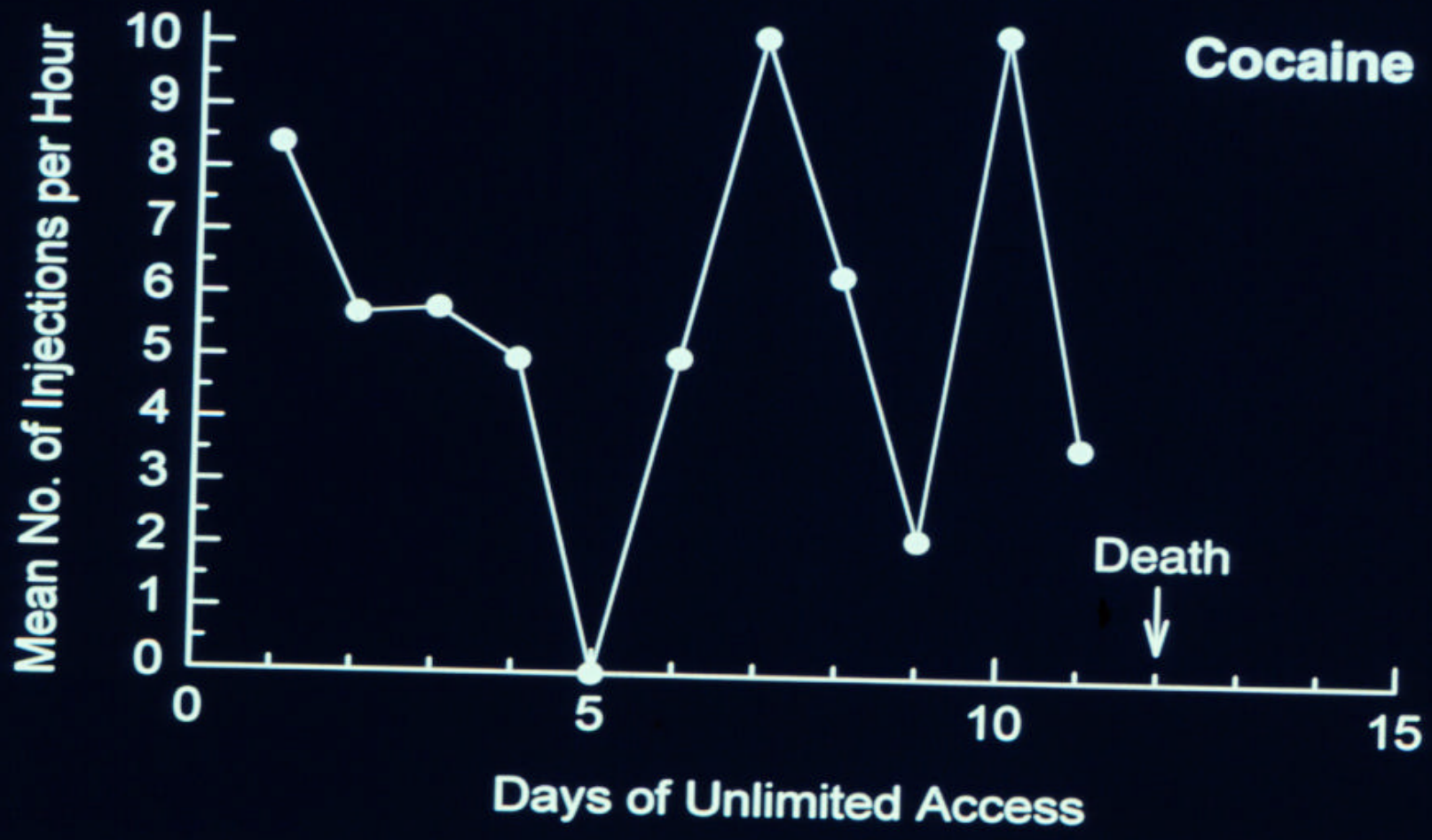
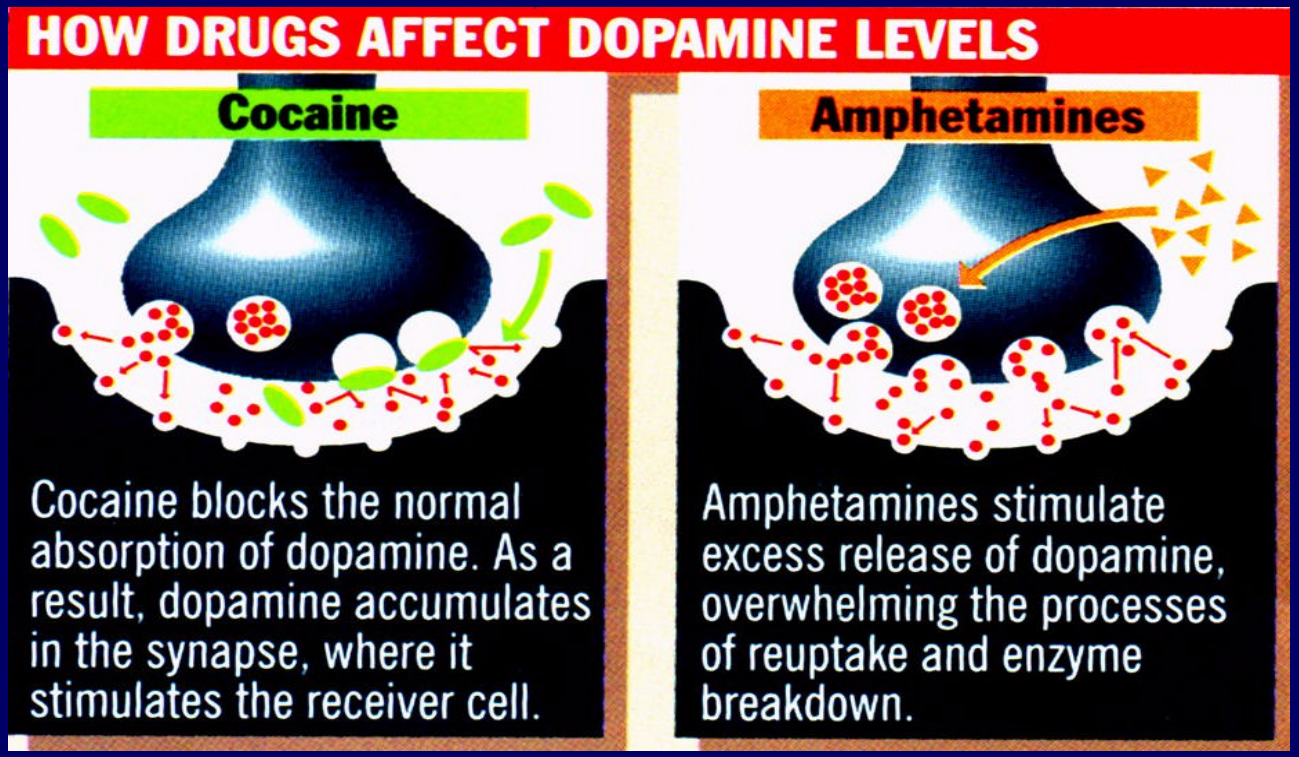


Fig 2. Daily intake of drug for typical subject self-administering cocaine hydrochloride, 1 mg/kg per infusion



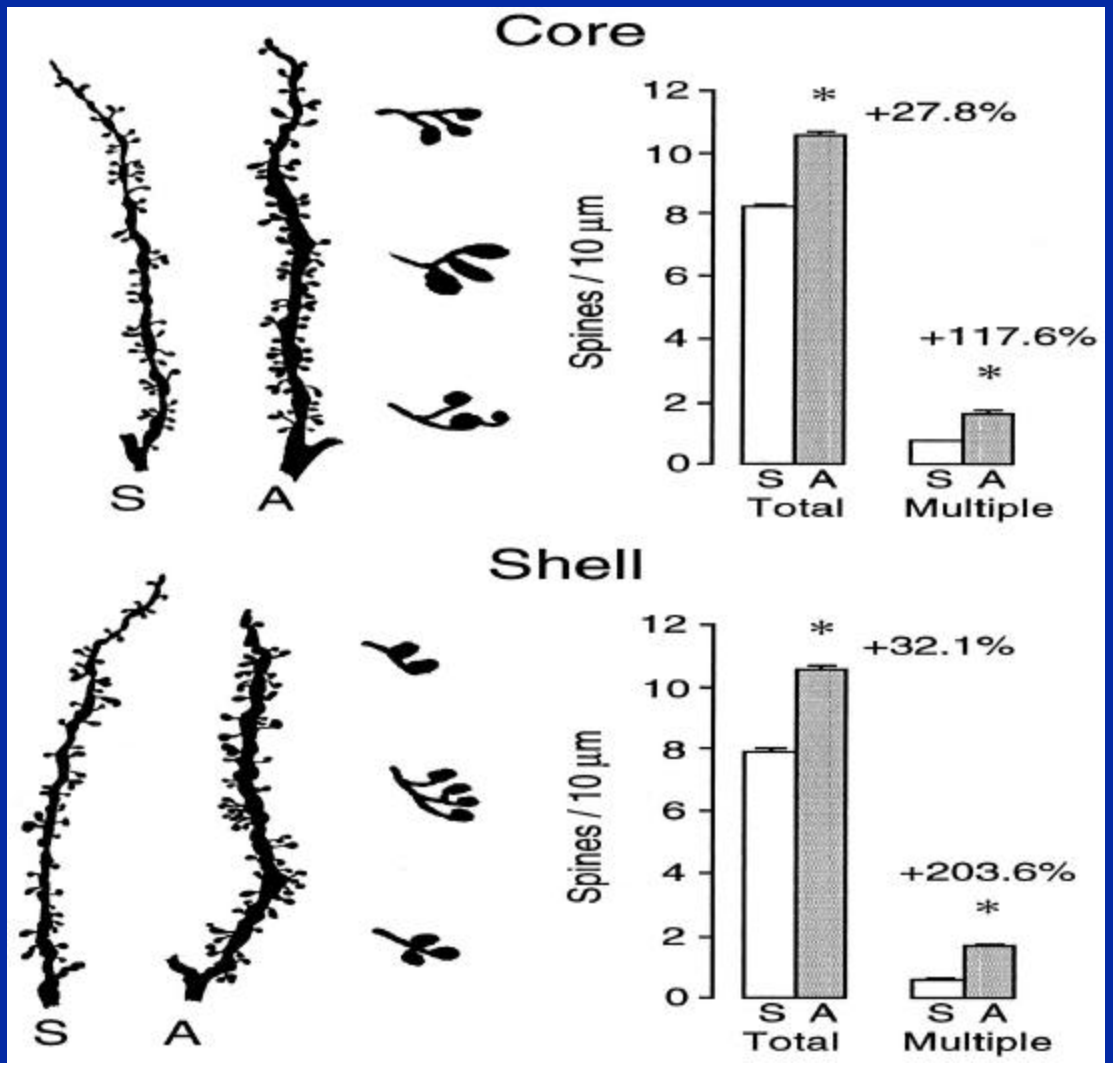
Different Effects
Same Pathway

***Time*, May 5, 1997**

Amphetamine: Pharmacodynamic Effects

- Marked euphoria associated with rate of DA increase
- Reinforces self-administration behavior, leading to repeated use
- Sensitization: re-exposure enhances effect→can lead to behavioral pathology e.g., paranoia, hallucinosis, automatisms lasting days
- Tolerance develops to euphoric effects
- Increased physical activity and parkinsonian tremor (lasts 3+ months)
- Mild tachycardia (10/min) and hypertension (20/10)
- Coronary vasodilation, then vasoconstriction; also platelet activation and coronary thrombosis, increasing risk of stroke and MI
- Neurotoxic at high doses; can last in monkeys up to 3 yrs.

Long-term amphetamine use increases dendritic spines in nucleus accumbens cells



S = saline
A= amphetamine

Cocaine and Amphetamines: Withdrawal

Controversial, even following high-dose use

- **Much of effect may be due to sleep deprivation, not drug**

Some reports of 3 phases: crash, depression, recovery

Drug Abuse Pharmacology: Summary

- **Dose, drug, route, and metabolism affect drug blood and tissue levels**
- **Binding to specific receptor starts intracellular chain of events, producing specific effects similar to those produced by natural ligands**
- **Chronic exposure and genetics alter individual responses to drugs and dependence symptoms**
- **Reinforcement pathways involving DA critical to repetitive drug use**